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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/284,615	06/25/99	TERSKIKH A	4-21101/A/PC

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/284,615	Applicant(s) Terstappen
	Examiner Ungar	Group Art Unit 1642

☒ Responsive to communication(s) filed on *Jul 10, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-33* is/are pending in the application.

Of the above, claim(s) *8-10 and 13-32* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-7, 11, 12, and 33* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The Election filed July 10, 2000 (Paper No. 7) in response to the Office Action of June 19, 2000 (Paper No. 6) is acknowledged and has been entered. Claims 1-33 are pending in the application and Claims 8-10 and 13-32 have been withdrawn from further consideration by the examiner under 37 CAR 1.142(b) as being drawn to non-elected inventions. Claims 1-7, 11-12 and 33 are currently under prosecution.

2. Applicant's election without traverse of Group I, claims 1-7, 11, 12 and 33 in Paper No. 7 is acknowledged.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

4. Claims 1-7, 11, 12 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth a BCL1/COMP pentabodies and therefore the written description is not commensurate in scope with the claims drawn to oligomers comprising at least two units wherein each unit comprises a

peptidic domain capable of oligomerizing and a domain capable of binding to an acceptor, wherein the oligomerizing domain is not an antibody.

Although drawn to the DNA art, the findings in *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111 are clearly applicable to the instant rejection. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111 clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Further, the findings of *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016, although drawn to the DNA art are also relevant to the instant rejection. *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016 find that adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required.

Finally, the findings of In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), although again drawn to the DNA art are relevant to the instant rejection. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not

required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

A review of the specification clearly demonstrates that applicant does not convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The specification teaches that claimed invention consists of a target molecule whose specificity can be provided by a short peptide ligand representing a minimal binding domain that binds to an acceptor, a hinge region which dictates the geometry and the dynamic feature of multivalent interaction and an oligomerizing domain. The specification further teaches that if coiled coil alpha helical domains are used the resulting oligomers are in most cases well soluble due to the intrinsic structure and the COMP domain can be used generally for oligomerization of the compounds bound thereto. The specification further teaches that "this is a general method for the oligomerization of peptides" (p. 2). An acceptor may be of various origins for example any protein that binds to an unlimited variety of binding partners (p. 3) and teaches that there are several ways to synthesize the inventive units (pgs 3-4) and exemplifies the synthesis of a BCL1/COMP oligomeric unit that spontaneously forms a pentamer (pages 8-12) wherein specific peptides that bind to anti-BCL_1 are selected, a 24

amino acid sequence is selected from a long camel Ig hinge region to provide a space necessary for multivalent binding, the hinge is followed by a 55 amino acid long pentamerization domain that is a modification of a known COMP assembly domain in order to further stabilize the bundle (p. 11). However, other than the single example of BCL1/COMP Pabs, there is no other example identified. Other than a modified COMP, there is no identification of any oligomerization domain that will function as contemplated. Other than for the specifically exemplified Pabs, there is no teaching of how to determine the type and length of spacer between the two components of the unit. Other than the specifically exemplified Pabs there is no complete or partial structure identified for the claimed oligomers. The single exemplified Pabs is not sufficient description of a representative number of species that would serve as a written description for the genus claimed. No disclosure, beyond the mere mention of other oligomers is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only BCL1/COMP Pabs, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

5. Claims 1-7, 11-12 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for oligomers wherein each unit comprises a COMP pentamerization domain as modified in the instant specification, a 24 amino acid sequence selected from a long camel Ig region as specifically exemplified in the instant application and an acceptor binding domain that is a

peptide that specifically binds to the exemplified B1 monoclonal antibody, does not reasonably provide enablement for an oligomer wherein each unit comprises a peptidic domain capable of oligomerizing and a domain capable of binding to an acceptor wherein the oligomerizing domain is not an antibody or a functional antibody fragment from a constant region. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The claims are drawn to oligomers whose units comprise a peptidic domain capable of oligomerizing and a domain capable of binding to an acceptor wherein the oligomerizing domain is not an antibody or a functional antibody fragment from a constant region. This includes a whole universe of units with an unlimited number of acceptors, unlimited oligomerization domains, connected either directly or by a whole universe of spacers. The specification teaches that the claimed invention consists of a target molecule whose specificity can be provided by a short peptide ligand representing a minimal binding domain that binds to an acceptor, a hinge region which dictates the geometry and the dynamic feature of multivalent interaction and an oligomerizing domain. The specification further teaches that if coiled coil alpha helical domains are used the resulting oligomers are in most cases well soluble due to the intrinsic structure and the COMP domain can be used generally for oligomerization of the compounds bound thereto. The specification further teaches that "this is a general method for the oligomerization of peptides" (p. 2) An acceptor may be of various origins for example any protein that binds to an unlimited variety of binding partners (p. 3). The specification teaches that there are

several ways to synthesize the inventive units (pgs 3-4) and exemplifies the synthesis of a BCL1/COMP oligomeric unit that spontaneously forms a pentamer (pages 8-12) wherein specific peptides that bind to anti-BCL_1 are selected, a 24 amino acid sequence is selected from a long camel Ig hinge region to provide a space necessary for multivalent binding, the hinge is followed by a 55 amino acid long pentamerization domain that is a modification of a known COMP assembly domain in order to further stabilize the bundle (p. 11). The specification also teaches that the pentamerization domain of COMP is known to spontaneously pentamerize (p. 3). One cannot extrapolate the teaching of the specification to the scope of the claims because other the specifically exemplified Pabs, there is no teaching of how to determine the oligomerization domain, the binding domain or the spacer between the two components of each unit. As drawn to the oligomerization region, it is clear that this region is of critical importance in the making of the instant invention since it is well known in the art that in many instances, oligomerization/aggregation leads to the precipitation of the oligomerized proteins. This is clearly exemplified in the specification, even using the modified COMP pentamerzation domain with PabD. Aggregation of the pentamer resulted in a reduction in the amount of soluble PabD to such an extent that the molecule was not used for additional experiments. Further, the solubility of the claimed oligomer appears to be essential to the ability to use the oligomer which as contemplated include its use as a targeting molecule, both *in vivo* and *in vitro*, an inhibitor, in complement fixation and activation or inhibition, as units in random peptide library displays. All of the contemplated uses for the claimed oligomer involve soluble oligomers. The critical nature of the solubility of

the pentamerization domain is demonstrated by Frank et al (Biochemistry, 2000, 39:6825-6831) who produced variants of phospholamban (PLB) which has a pentameric transmembrane domain but is not soluble. These variants were produced by combining the surface residues of COMP (which contain mostly hydrophilic amino acids) and the hydrophobic interior of the transmembrane domain of PLB. Although it is clear that the pentamerization domains are known in the art, the specification does not teach how to determine which ones, other than that of COMP, could be used to make the invention so that it would function as contemplated. Further, there is no teaching on how to determine what type of spacer to use for each of this universe of claimed molecules. Although drawn to the single chain antibody art the teaching of Klausner (Bio/technology, 1986, 4:1042-1043 and Williams (TIBS, 1988, 6:36-40) are relevant to the instant rejection. Williams teaches the production of single chain antibodies by linking variable regions of heavy and light chains (2 units) of an antibody by a synthetic peptide linker. The binding sites of the variable domains are dependent upon the accurate positioning of the heavy and light chain variable domains with respect to each other. The reference teaches that for this reason it is essential for the peptide linker that holds them together to be carefully designed to ensure that it does not interfere with the correct folding of the molecule (p. 39, col 2). Klausner teaches that in order to properly position the antibody fragments, the protein linker needs to span about 30-40 angstroms. This would require 15-25 amino acids, the exact number would depend on the extent to which the linker takes on a secondary structure of its own. There are potential advantages and disadvantages to linker configurations and it is

difficult to predict which will work best. Klausner goes on to list difficulties that must be worked out for linkers including interference with proper molecule folding, producing molecules with an increased susceptibility to proteolysis (p. 1043, col 1). It is clear that the specification, other than for the specifically exemplified molecules, does not teach methods of producing or screening spacers for linking the domains of the claimed molecules so that they will function as claimed. It is equally clear that the art teaches that the proper spacer is critical to the function of bispecific molecules such as that claimed. It cannot be predicted, based on the information in the specification or in the art, which spacers, or what design spacers, can be used for the broadly claimed invention in order to produce molecules that will both oligomerize/pentamerize and bind to their acceptors. Further, the claims are drawn to units that pentamerize. However, other than the COMP pentamerization region that spontaneously oligomerizes, no other oligomerizing domain is taught. There is no teaching of how to produce oligomerization/pentamerization if the units do not spontaneously pentamerize. In addition, it is clear, as taught by Kajava (IDS item AQ) that it cannot be predicted or be expected that all oligomerization domains will pentaoligomerize, that is form a five stranded structure rather than a two or three stranded structure. Kajava specifically teach that the COMP structure has some specific features that explain why COMP forms a pentamer and not a dimer, trimer or tetramer (p. 225, col 1). Further, although the specification teaches linker molecules bearing two or more reactive groups, there is no teaching of how or where to attach these groups to oligomerization domains so that the molecule produced will function as claimed. In the absence of specific guidance provided in

the specification as to which oligomerization domains, which spacer domains and which binder domains could be joined to make the invention as claimed, the skilled artisan is left to randomly experiment from the universe of domains claimed in order to determine which combination would function as claimed. Such random trial and error experimentation is considered to be undue. In view of the above, one of skill in he art would be forced into undue experimentation to practice the claimed invention.

6. Claims 1-7, 11-12 and 33 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7, 11-12 and 33 are indefinite because claims 1 and 6 recite the term "peptidic". The claims are indefinite because there is no art recognized meaning for the term and the metes and bounds of the claims cannot be determined

Claim 11 is drawn to the pentamerization domain of cartilage oligomeric matrix protein. The claims are objected to as being indefinite in the use of designation cartilage oligomeric matrix protein as the sole means of identifying the claimed antibodies. The use of laboratory designations only to identify a molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely molecules. Although cartilage oligomeric matrix protein is known in the art, it is also known that splice variants and mutated versions of the protein are known. Amendment of the claims to include unique identifiers of the protein would obviate this rejection.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-6 and 11-12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Efimov et al (FEBS Letters, 1994, 431:54-58, IDS item AO).

The claims are drawn to an oligomer comprising at least 2 units, 4 units, 5 units wherein each unit comprises a peptide domain capable of oligomerizing and a domain capable of binding to an acceptor wherein the oligomerizing domain is not an antibody, wherein each unit is less than 600 amino acids, wherein the oligomerizing domain is the pentamerization domain of cartilage oligomeric matrix protein and wherein the units bind distinct acceptors/receptors.

Efimov et al teach an oligomer made of five units (see abstract) wherein each unit has less than 600 amino acids, (see Fig 4), that is 65 residues (See p. 57, col 1), which are pentamerized with the oligomerization of the cartilage oligomeric matrix protein pentamerization domain wherein the peptide domain is capable of oligomerising. This domain, an acceptor, is capable of binding to an identical domain, a receptor, both of which are connected via disulphide bridges, a spacer. It would be expected that the units would bind distinct acceptors, i.e. polyclonal antibodies specific for the units.

9. Claims 1-5 and 11-12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Morgelin et al (JBC, 1992, 267:6137-6141).

The claims are drawn to an oligomer comprising at least 2 units, 4 units, 5 units wherein each unit comprises a peptide domain capable of oligomerizing and a domain capable of binding to an acceptor wherein the oligomerizing domain is not an antibody, wherein each unit is less than 6000 amino acids, wherein the oligomerizing domain is the pentamerization domain of cartilage oligomeric matrix protein and wherein the units bind distinct acceptors/receptors.

Morgelin et al teach an isolated cartilage oligomeric matrix protein which is a bouquet-like protein which consists of five 28 nm long arms containing a peripheral globular domain (the binding domain), a flexible strand (the spacer)and a central assembly domain (the pentamerization domain) where the five arms meet in a cylindrical structure. It would be expected that the binding domains would bind distinct acceptors, i.e. polyclonal antibodies specific for the domains.

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
September 25, 2000